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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,950	08/18/1999	TOMMY EKSTROM	06275/188001	4952

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,950	EKSTROM, TOMMY	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-36,38,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-36,38,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed June 29, 2005 have been received and entered into the application.

Action Summary

The rejection of claims 13, 35, 36 and 42 under 35 U.S.C. 112, first paragraph is maintained for the reasons stated in the previous Office Action.

The rejection of claims 13-15, 17, 18, 20-36, 38 and 42 rejected under 35 U.S.C. 103 (a) as being unpatentable over Carling of record is being maintained for the reasons stated in the previous Office Action and the rejection is modified to include newly added claim 43 in this Office Action.

The rejection of claims 16 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. of record as applied to claims 13-15, 17, 18, 20-36 and 42 and further in view of Aberg et al. (U.S.Patent No. 5,795,564) and Ryrfeldt et al. of record is being maintained for the reasons stated in the previous Office Action and the rejection is modified to include newly added claim 43 in this Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 13, 35, 36 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of an acute episode of asthma", does not reasonably provide enablement for the "prevention of an acute episode of asthma". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating or **preventing** an acute episode of asthma in a patient with an effective amount of a composition comprising formoterol and budesonide that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a **preventive** measure,

when the patient experiences an increase in symptoms of an acute episode of asthma. The nature of the invention is extremely complex in that it encompasses the actual prevention of an acute episode of asthma such that the subject treated with above composition does not contract an acute episode of asthma.

Breath of the Claims: The complex of nature of the claims

Greatly exacerbated by breath of the claims. The claims encompass prevention of a complex cell autoimmune disorder in humans which has potentially many different causes (i.e. many different allergen or combination of allergens). Each of which may or may not be addressed by the administration of the claimed composition.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed composition to a subject in order to actually prevent an acute episode of asthma is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of an acute episode of asthma.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of an acute episode of asthma.

State of the Art: While the state of the art is relatively high with regard to treatment of an acute episode (i.e. acute asthmatic attack), the state of the art with regard to prevention of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a

composition similar to the claimed compounds was administered to a subject to prevent development of an acute episode of asthma.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual prevention of an acute episode of asthma in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of an acute episode of asthma.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **prevention** of an acute episode of asthma. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of an acute episode of asthma with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of an acute episode of asthma with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require

undue, unpredictable experimentation to practice the claimed invention to prevent the development of an acute episode of asthma in a subject by administration of the claimed composition.

Therefore, a method of **preventing** an acute episode of asthma in a patient in need thereof administering composition comprising formoterol and budesonide that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a **preventive** measure, when the patient experiences an increase in symptoms of an acute episode of asthma is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 13-15, 17, 18, 20-36, 38, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling of record.

Carling et al. on page 6, lines 5-30, teach the suitable daily asthmatic dose of formoterol fumarate dihydrate as required by claim 15 and budesonide within Applicant's daily dosage of "on demand" (twice a day) and the dosages strongly depends on the patient (age, weight etc.), severity of disease (mild, moderate, severe asthma etc..).

Carling et al. on pages 7-9 exemplify amounts of active agents per dose of inhalation, which calculate up to 8 inhalation per day without going over the maximum daily dosage.

Carling teaches at page 8-14, page 3, line 35 through page 4, line 10, lines 30-35, page 6, lines 5-30, and page 7, lines 1-5, teach a composition comprising Applicant's active agents use for treating respiratory disorder such as asthma set forth in claims 13-15, 17-18, 20-21, and 23.

Carling et al. at page 4, lines 3-10, also teach that the combination of formoterol and budesonide has not only a greater efficiency and duration of bronchodilator action but also a rapid onset of action.

The difference between Carling et al. and Applicant's invention is instructing a patient to inhale, on demand, as determined by the patient based on the patient's symptoms, to provide short-term symptomatic relief of acute asthmatic symptoms set forth in claims 13 and 36, instructing patient to inhale additional doses as needed if he experiences asthma including acute asthmatic episode, a specific carrier set forth in claim 24, the molar ratio of active agents set forth in claim 14, and the particle size set forth in claim 22.

However, to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling et al. teach that the dosages strongly depends on the severity of disease (mild, moderate, severe asthma) and the suitable daily dosage is up to 8 inhalation. One of ordinary skill in the art would be motivated to instruct those patient with severe asthma or acute asthmatic

attack to use the Carling's composition as needed bases up to 8 inhalations as suggested by Carling et al. that the dosages strongly depends on the severity of disease and to achieve maximum benefit of daily dosage recommended by Carling et al. It is noted that combination of formoterol with budesonide is well known to be beneficial for the treatment of asthma as taught by Carling et al. Moreover, if that patient experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, he still can safely inhale additional 6 inhalations without going over the maximum suitable daily dosage in general asthmatic condition taught by Carling et al. to achieve its known therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition.

The molar ratio of active agents to be used set forth in claim 14, the selection of carrier set forth in claims 23 and 24, and the particle size of active agents set forth in claim 22, are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations.

Claim 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. of record as applied to claims 13-15, 17, 18, 20-36, 38, 42 and 43 above, and further in view of Aberg et al. (U.S.Patent 5,795,564) and Ryrfeldt et al. of record.

Carling et al. as applied as before.

Carling et al. do teach the isomer of formoterol set forth in claim 16 and the specified epimer of budesonide set forth in claim 19.

Aberg et al. teach (R, R) isomer of formoterol as required by claim 16 is a potent bronchodilator with reduced adverse effects in treatment of asthma. (abstract, column, 1, lines 25-35).

Ryrfeldt et al. teach that 22R epimer of budesonide is more potent in the treatment of bronchial asthma than 22S epimer.

However, it would have been obvious to one of ordinary skill in the art to employ (R, R) enantiomer of formoterol and 22 R epimer of budesonide in view of Aberg et al. and Ryrfeldt et al. because both of the references of Aberg and Ryrfeldt teach specific isomers form that possesses potent asthmatic effect of the active agents utilized in Carling reduced adverse effects in treatment of asthma. One would have been motivated to employ (R,R) isomer of formoterol and 22R epimer of budesonide in Carling's composition with reasonable expectation of successfully treating asthmatic patients with reduced adverse effects.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

Response to Arguments

Applicant's arguments filed June 29, 2005 have been fully considered but they are not persuasive. Applicant essentially argues Exhibits teach each and every one of the doses to be administered as "twice daily" and there is no provision for additional doses to be taken "as needed" and regardless of whether the patient is feeling better or worse on a given day the patients should not to take more or less than the exact dose prescribed by the physician. This is not persuasive because Carling et al. teach by the examples on pages 7-9 the amounts of the active agents in combination to be used per day. The maximum dosage amounts taught by Carling et al. allows up to 8 daily inhalations of the combination (budesonide/formoterol) to the asthmatic patients. With regard to Applicants' limitation of daily dosage of "on demand", it is the Examiner's position that one of ordinary skill in the art would be motivated to instruct the patient to use the combination of budesonide and formoterol taught by Carling within the therapeutic dosages recommended by Carling et al. up to the maximum and without going over in the event of an asthmatic attack as experienced by the patient because Carling teaches the maximum daily dosages not restricted to the amount required by "twice a day", rather, the total maximum daily dosage that is safe and effective for the asthmatic treatment. Applicant argues if the patient suffers an exacerbation of symptoms, he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief: "PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma. This is not persuasive because PULMICORT TURBUHALER only consists of single active agent, budesonide (a corticosteroid). Applicant's exhibit A (D) teaches that PULMICOR

TURBUHALER is not indicated for rapid relief of bronchospasm or other acute episodes of asthma because PULMICOR TURBUHALER is not a bronchodilator. Applicant is remained that Carling teaches the combination of formoterol (bronchodilator) and budesonide in a single formulation for the treatment of asthma. It is noted that formoterol exerts a prolonged bronchodilation in clinical trials up to 12 hours. (page 2, lines 25-27 of Carling et al.). Therefore, exhibit A (D) does not negate the use of the combination of Carling (budesonide and formoterol (bronchodilator)) for the treatment of acute episodes of asthma because formoterol is a bronchodilator and exerts prolonged bronchodilation up to 12 hours. Therefore, it would be obvious to one of ordinary skill in the art to use the combination taught by Carling et al. for the acute asthma attack since the combination includes bronchodilator (formoterol) as one of the active agent. Applicant argues since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose and the warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly but not short-term relief of acute symptoms. This is not persuasive because the exhibit A (D) and (F), only consists on one active agent budesonide not in combination with formoterol as taught by Carling et al. The warning set forth in exhibit A (F) shows the potential adverse effect of "OVERDOSAGE" for prolonged periods which does not negate the use of Carling's combination of formoterol and budesonide because

Carling's dosages are within the therapeutic range that is "recommended" by Carling's and it is effective and safe for the treatment of asthma **not** "OVERDOSAGE" as indicated in the Exhibit A (F). Applicant argues that Exhibits B is a product insert for the combination of budesonide/formoterol inhalation product (SYMBICORT TURBUHALER), and the "recommended dosage" is 1-2 inhalations twice daily and this instruction instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease. This is not persuasive because while the instruction of the SYMBICORT product recommends' 1 to 2 times day to instruct the physician and to have physician to adjust the dosage to reflect the severity of the particular patient's disease, Carling et al. recommends maximum daily dosage to be instruct by the physician to reflect the severity of the particular patient's severity of asthma. Therefore, one of ordinary skill in the art, physician would modify the teaching of Carling et al. to instruct the patient to employ the combination taught by Carling within the maximum daily dosage as needed when the attack experienced **by the** patient to alleviate the patient's asthmatic attack. Applicant further argues that a journal article (O'Byrne et al.) discusses the positive results of a recent clinical trial studying the efficacy of the clamed method in providing rapid symptoms relief and simultaneous adjustment in anti-inflammatory therapy thereby reducing the incident of exacerbations. This is not persuasive because the O'Bryne et al' method of twice a day and as need is encompassed by Carling et al. because Carling teaches maximum daily dosages of the combination exceeding twice a day amounts. Applicant argues regarding rejections under 35 U.S.C. 112 first paragraph, the Applicant essentially argues that the

specification provides ample guidance in how to prevent an acute episode of asthma and it is common to day "prevent' the symptoms or the exacerbations (i.e. acute episodes) when the anti-inflammatory agents such as budesonide have long been used as "maintenance" drugs to control symptoms and reduce the number of exacerbations experienced by the patient, regardless of the underlying triggering cause. This is not persuasive because the guidance provided by the specification is directed toward the treatment rather than prevention of an acute episode of asthma and all working examples provided by the specification are directed toward the treatment rather than prevention of an acute episode of asthma and what is used "common" to day, does not make the treatment of asthma to be absolute "prevention". Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

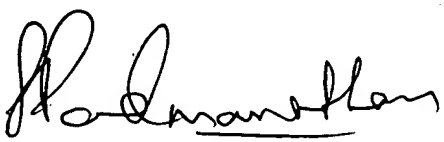
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
September 16, 2005